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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,643	11/18/2003	Peter A. Crooks	069962-0102	2532

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EXAMINER	
CHONG, YONG SOO	
ART UNIT	PAPER NUMBER
1617	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/714,643	CROOKS ET AL.	
	Examiner	Art Unit	
	YONG S. CHONG	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-7,9,10,13-17,28,71 and 73-83* is/are pending in the application.

4a) Of the above claim(s) *73-79 and 81-83* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-7,9,10,13-17,28,71 and 80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/15/08, 7/31/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

This Office Action is in response to applicant's arguments filed on 7/15/08. Claims 3-4, 8, 11-12, 18-27, 29-70, 72 have been cancelled. Claims 1-2, 5-7, 9-10, 13-17, 28, 71, 73-83 are pending. Claims 73-79, 81-83 have been withdrawn. Claims 1-2, 5-7, 9-10, 13-17, 28, 71, 80 are examined herein.

Applicant's arguments have been fully considered but found not persuasive. The rejection of the last Office Action is maintained for reasons of record and repeated below for Applicant's convenience.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham vs John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-2, 5-7, 9-10, 13-17, 28, 71, 80 are rejected under 35 U.S.C. 103(a) as being obvious over Harbut et al. (US Patent Application 2005/0148673 A1) in view of Ebert et al. (European Journal of Pharmacology, 333, 1997, 99-104).

The instant claims are directed to a method of treating neuropathic pain in an patient in need thereof comprising administering substantially enantiomerically pure (S)-norketamine over a 24-hour period and in conjunction with a narcotic analgesic effective to treat pain.

Harbut et al. teach treating neuropathic pain by administering a composition comprising NMDA receptor antagonist, such as ketamine (abstract), which can be co-administered with Valium (paragraph 0033). Ketamine can be administered intravenously and subcutaneously (paragraph 0038) and for a sustained period of time, such as two or more consecutive days (paragraph 0057). Ketamine is also disclosed to be metabolically degraded into norketamine, which is about 25% as effective as ketamine (paragraph 0081). Other pain treating drugs, such as morphine and oxycontin, were typically reduced by about 25% on the second day of treatment, while ketamine treatment continued (paragraph 0086). Typical dosage of ketamine is disclosed to be 10 mg/hour (paragraph 0100) or 240 mg per day, which meet the limitation between 0.05 to 8 mg/kg body weight or 3.5 to 1400 mg for an average adult of 70 kg.

Harbut et al. teach as discussed above, however fail to specifically disclose (S)-norketamine.

Ebert teaches that ketamine is taught to be a well-known NMDA receptor antagonist and has been used as an analgesic for over 30 years. In sub-anaesthetic doses the analgesic effects of ketamine are thought to be mediated by the blockade of the NMDA receptors. Norketamine is a metabolite of ketamine with similar pharmacological profiles as a NMDA receptor antagonist following an oral or i.m. dose (pg. 99-100). Therefore, norketamine has some analgesic properties. It was determined that (S)-norketamine contributes significantly to the clinical activity of (S)-ketamine (abstract). It was also determined that (S)-norketamine is approximately 8 times more potent than (R)-norketamine (pg. 102). Following oral administration of (RS)-ketamine, (S)-norketamine will be present in human plasma at sufficiently high concentrations to account for some of the observed analgesic activity. Clinical studies involving oral administration of (S)-norketamine and its reduced side effects are now being investigated in humans (pg. 103).

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed invention was made, to have substituted substantially enantiomerically pure (S)-norketamine as disclosed by Ebert for the ketamine in the method for treating neuropathic pain as disclosed by Harbut.

A person of ordinary skill in the art would have been motivated to substitute substantially enantiomerically pure (S)-norketamine as disclosed by Ebert for the ketamine in the method for treating neuropathic pain as disclosed by Harbut because: (1) both (S)-norketamine and ketamine are functionally equivalent as NMDA receptor antagonists; (2) both (S)-norketamine and ketamine are known in the prior art to have

analgesic properties; (3) ketamine breaks down metabolically to (S)-norketamine; (4) (S)-norketamine is disclosed to have fewer side effects than ketamine; (5) (S)-norketamine contributes significantly to the clinical activity of (S)-ketamine; and (6) (S)-norketamine is approximately 8 times more potent than (R)-norketamine. Therefore, the skilled artisan would have had a reasonable expectation of success in treating neuropathic pain by administering a composition comprising substantially enantiomerically pure (S)-norketamine. Furthermore, it is obvious to one of ordinary skill in the art to have self-administered on an outpatient basis, substantially enantiomerically pure (S)-norketamine, to effectively treat neuropathic pain because of the convenience and ease of not having to go to the hospital as frequently and for prolonged periods of time.

Examiner notes that the dosage amounts disclosed in the rejection is inherently below a level to induce dysphoria as well as in a range of about 10 to about 20% of an amount used to induce anesthesia since a composition and its properties are inseparable. It is also obvious that a physician or medical provider would prescribe such dosages so as to limit or reduce as much side effects as possible.

"Products of identical chemical composition can not have mutual exclusive properties." Any properties exhibited by or benefits from are not given any patentable weight over the prior art provided the composition is inherent. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the disclosed properties are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. The

burden is shifted to the applicant to show that the prior art product does not inherently possess the same properties as the instantly claimed product.

Response to Arguments

Applicant argues that the submitted Declaration by Dr. Kleven as well as Exhibit 1 demonstrates unexpected results, which overcome the 103(a) obviousness rejection. Specifically, the Declaration shows (S)-norketamine, given at equipotent dosage, results in an unexpected reduction of side effects in comparison to an equipotent dosage of racemic ketamine.

The Kleven Declaration under 37 CFR 1.132 filed 7/15/08 is insufficient to overcome the rejection of claims 1-2, 5-7, 9-10, 13-17, 28, 71, 80 based upon Harbut et al. (US Patent Application 2005/0148673 A1) in view of Ebert et al. (European Journal of Pharmacology, 333, 1997, 99-104) as set forth in the last Office action.

Applicant's assertion that the unexpected reduction of side effects is incorrect because this property is known in the prior art, therefore considered to be expected. In fact, the cited prior art reference above, Ebert, teaches that clinical studies involving oral administration of (S)-norketamine are accompanied with reduced side effects in humans. Applicant is reminded that (S)-norketamine is already known for its reduced side effects, therefore the Kleven Declaration shows nothing unexpected.

In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

Applicant argues that there is no motivation to combine Harbut with Ebert because norketamine is mentioned only four times by Harbut. Applicant points to various places in Harbut that mentions the disadvantages of administering ketamine including intolerable side effects. Harbut teaches away because norketamine is taught to be less effective than ketamine.

This is not persuasive because Harbut was not relied on for the teaching of norketamine. The fact that norketamine is mentioned only four times does not take away from the teaching by Ebert that (S)-norketamine is approximately 8 times more potent than (R)-norketamine and with fewer side effects. Applicant is reminded that Ebert provides clear and convincing motivation to substitute the more potent (S)-norketamine for the racemic ketamine taught by Harbut.

In response to applicant's arguments against the references, one cannot show nonobviousness by attacking references individually where the rejections are based on the combination of references. See *In re Keller*, 642 F. 2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F. 2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant argues that not all of the claimed elements are taught or suggested by the prior art, specifically the limitation concerning "the administration range is about 0.01 to about 20 mg/kg of body weight of the patient." Applicants contend that this dosage amount is not suggested in either Ebert or Harbut for norketamine.

This is not persuasive because Harbut clearly teaches the typical dosage for ketamine is 10 mg/hour (paragraph 0100) or 240 mg per day, which meet the limitation between 0.05 to 8 mg/kg body weight or 3.5 to 1400 mg for an average adult of 70 kg.

Applicant is reminded that the obviousness rejection was formulated to substitute (S)-norketamine as taught by Ebert for the ketamine in the method for treating neuropathic pain as taught by Harbut.

Finally, Applicant argues against the cited *In re Spada* case law as it applies to the limitation "effective to treat pain while not inducing dysphoria" because the holding of *In re Spada* was related to composition claims, not method claims.

This is not persuasive because the method claims involve the use of a composition comprising active agents. Nonetheless, Applicant is invited to provide factual data showing that the same composition as rendered obvious by the cited prior art does not have this property of effectively treating pain while not inducing dysphoria, while the same instantly claimed composition possesses this property.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong S. Chong whose telephone number is (571)-272-8513. The examiner can normally be reached on M-F, 9-6.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SREENI PADMANABHAN can be reached on (571)-272-0629. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Yong S Chong/
Examiner, Art Unit 1617

YSC